Amendments to the Drawings:

The attached sheets of drawings includes changes to Figs. 3 and 12. These sheets, which includes Figs. 3 and 13 replace the original sheets including Fig. 3 and 12.

The attached sheets of drawings also add Figs. 15-18. These sheets, which includes Figs. 15-18 replaces the schemes originally presented in the specification.

Attachment: Annotated Sheets Showing changes

New Sheets

REMARKS/ARGUMENTS

I. Status of the Claims

Upon entry of the present amendment, claims 71 and 118-132 are pending in the application and presented for examination. Claim 71 is currently amended, claims 118-132 are new and claims 1-70 and 72-117 are canceled. New claims 118-132 recite subject matter of elected Group I and find support in the original claims. The following table shows the correspondence between the previously pending claims and the new claims.

Pending Claim	New Claim
71	71
58	118
59	119
105	120
106	121
107	122
108	123
109	124
110	125
111	126
112	127
113	128
114	129
115	130
n/a	131
116	132

New independent claim 118 is based on previously pending claim 58, where R^1 is adamantyl; P^1 is –NHC(O)NH-; n is one; and m is one. Support for these amendments can be found in the specification at paragraphs [0069]-[0076].

New independent claim 119 is based on previously pending claim 59, where R^1 is selected from aryl or heteroaryl.

New independent claim 131 is based on previously pending claim 58, where R^1 is adamantyl; P^1 is –NHC(O)NH-; n is zero; m is one; and L^1 and L^2 combine to form a linker of 11 or 12 carbon alkylene chain. Support for these amendments can be found in the specification at paragraphs [0069]-[0076]. Support of the linker chain being 11 or 12 carbons, can be found in paragraph [0075] which recites the preferred number of carbons for L^1 and L^2. This paragraph states that "when L^1 is an alkylene or part of a cycloalkylene linkage of from 2 to 4 carbon atoms, and P^2 is not present, L^2 will be preferably be an alkylene linkage of...8 carbon atoms."

No new matter is added by these amendments to the claims.

II. Amendments and Objections to the Drawings and Specification

The Examiner has objected to Figures 3 and 12 as being too dark to discern the details of the images. In response, Applicants submit herewith replacement Figures 3 and 12, which correspond to the original figures.

In addition, the Examiner has objected to the specification as having synthetic schemes which should be placed with the drawings. In response, Applicants submit herewith new Figures 15-18, which correspond to Schemes 1-4 found in the Examples as set forth in the instant specification. Applicants have also amended the specification to delete the corresponding schemes, including Schemes 1-4 and to replace each reference to a synthetic scheme with a reference to the corresponding new figure. Applicants have also amended the specification to add a reference to the new figures under the section "Brief Description of the Drawings".

No new matter is added by these amendments to the specification. Thus, Applicants respectfully request that the objection to the specification be withdrawn.

III. Information Disclosure Statement

The Examiner has requested that copies of References 1 and 2 (WO 00/48593 and WO 03/061597, respectively) from the IDS be provided. Copies of these references are attached.

IV. Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 107-109 under 35 U.S.C. § 112, second paragraph for allegedly lacking antecedent basis. The Examiner also rejected Claim 114 under 35 U.S.C. § 112, second paragraph for referring to tables in the Specification. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

Previous claims 107-109 correspond to new claims 122-124, respectively, which have proper antecedent basis. Previous claim 114 corresponds to new claim 129 which recites the structures of compounds from Tables 1-14 within the scope of the present claims. Accordingly, Applicants respectfully request that these rejections be withdrawn.

V. Rejections under 35 U.S.C. § 102 over Morisseau

The Examiner rejected Claims 58, 59, 105-109, 111-114, and 116 under 35 U.S.C. §102(a) as being allegedly anticipated by Morisseau *et al.* (Biochem. Pharm (2002) 63, pages 1599-1608; "Morisseau"). To the extent the rejections apply to the amended claims, Applicants respectfully traverse the rejection.

Applicants submit herewith an *In re Katz* Declaration Under 37 C.F.R. § 1.132, which establishes that Morisseau describes the inventors' own work, as disclosed in priority application, USSN 60/460,559, filed April 3, 2003. The declaration is executed by Drs. Morisseau and Hammock, joint inventors of the present application, but is unsigned by Dr. Newman, who is currently unavailable. A fully executed *Katz* declaration will be resubmitted

shortly. Accordingly, the Applicants contend that Morisseau is not prior art under 35 U.S.C. § 102(a or e). Withdrawal of the rejection is respectfully requested.

VI. Rejections under 35 U.S.C. § 102 over Richter

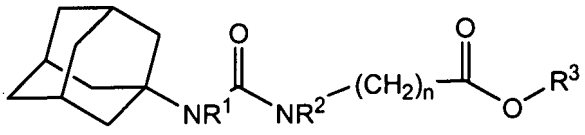
The Examiner rejected claims 58, 59, 105-109, and 111-113 under 35 U.S.C. §102(a) as being anticipated by Richter *et al.* (U.S. Patent No. 3703537, "Richter"). The Examiner also rejected Claims 58, 59, 105-109, and 111-113 under 35 U.S.C. §102(b) as being anticipated by Richter *et al.* (CAS Accession number 71: 18417, "Richter"). Applicants note this CAS Accession number refers to the same reference, U.S. Patent No. 3,703,537. To the extent the rejections apply to the amended claims, Applicants respectfully traverse the rejection.

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California,* 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). *See also* M.P.E.P. § 2131. In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

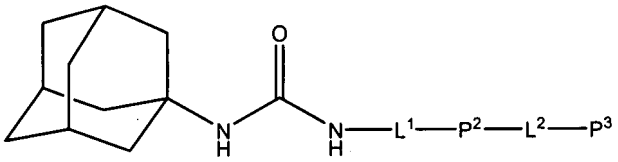
Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention. Applicants traverse the instant rejections.

The Examiner alleges that Richter discloses compounds of the formula I-b:



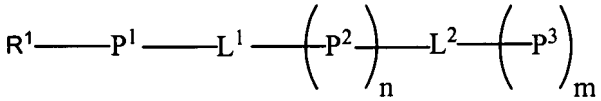
where **Alk is a straight or branch chained saturated alkyl of from 1 to 10 carbons**. In the above formula R^1 and R^2 are H or lower alkyl; R^3 is a member selected from the group consisting of hydrogen, a straight or branch chained saturated alkyl of from 1 to 12 carbons, di-(lower alkyl)-amino-lower alkyl, benzyl, 4-(N-methyl)-piperidyl and an alkoxy group of the formula: R'-(O-R")$_n$-O-R"', where R', R', and R"' are each a member selected from the group consisting of methyl and ethyl, and n is an integer from zero to three. Applicants assert that Richter fail to teach all of the elements of the claimed invention.

Applicants respectfully point out to that independent claim 118 recites a compounds having the formula:



wherein $-P^2-L^2-P^3$ is **not** a straight or branch chained saturated alkyl of from 1 to 10 carbons.

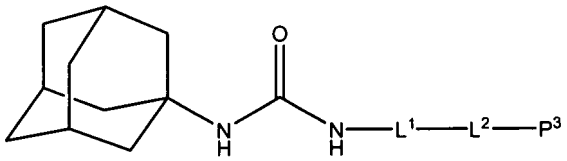
Likewise independent claim 119 recites compounds having the formula



(I)

wherein R^1 is aryl or heteroaryl and **not** adamantyl.

Finally, independent claim 131 recites compounds



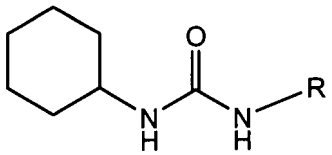
wherein L^1-L^2 is an unsubstituted or substituted alkylene linker of 11 or 12 carbons and **not** 1 to 10 carbons. Because Richter does not disclose compounds corresponding to the structural formulas of the pending claims, this reference does not anticipate the presently claimed compounds because each and every element as set forth in the claims is not found

therein. Accordingly, Applicants respectfully request that the Examiner withdraw these rejections under 35 U.S.C. § 102(a and b).

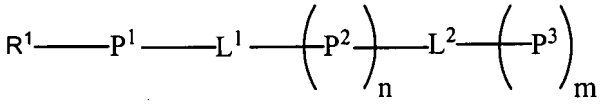
VII. Rejections under 35 U.S.C. § 102 over Kroetz I and II

The Examiner rejected Claims 58, 59, 105-109, and 111-114 under 35 U.S.C. §102(b) as being anticipated by Kroetz et al. (U.S. Patent No. 6,531,506; "Kroetz I") and under 35 U.S.C. §102(e) as being anticipated by Kroetz et al. (U.S. 2004/0092487; "Kroetz II"). To the extent the rejections apply to the amended claims, Applicants respectfully traverse the rejection.

The Examiner alleges out that Kroetz I and II disclose various compounds having the formula:



which correspond to compounds of formula I:



(I)

wherein R^1 is a cyclohexyl group.

Applicants point out that the amended claims do not have a cyclohexyl group in the R^1 position of formula I. As a result, these references do not anticipate the presently claimed compounds because each and every element as set forth in the claims is not found therein. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. § 102(b and e).

VIII. Rejections under 35 U.S.C. § 103 over Morisseau

The Examiner rejected Claims 58, 59, 70, 105-109, 111-114, and 116 under 35 U.S.C. §103(a) as allegedly being unpatentable over Morisseau. Applicants respectfully traverse this rejection. For the reasons discussed above, Morisseau is not proper art for use in the present

rejection. Because Morisseau is not proper art against the present invention, the Examiner is respectfully requested to withdraw this rejection.

IX. Rejections under 35 U.S.C. § 103 over Richter in view of Brocchini and Abdulla

The Examiner rejected Claims 58, 59, 70, 105-109, 111-114, and 116 under 35 U.S.C. §103(a) as allegedly being unpatentable over Richter, in view of Brocchini (U.S. Patent No. 5,877,224) or Brocchini and Abdulla (U.S. Patent No. 4,252,954). To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

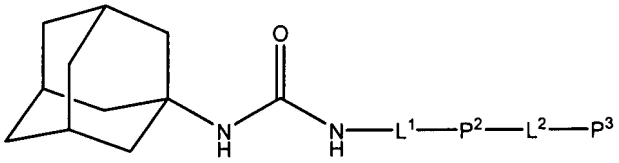
Recently, while cautioning against the rigid application of the teaching, suggestion, motivation (TSM) test, the Supreme Court affirmed the analysis set forth in *Graham* for the determination of obviousness. *See KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Specifically, the Supreme Court, quoting from *Graham*, stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject is determined. Such secondary considerations as commercial success, long felt but unresolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *Id.* at 1734.

The Court went on to state that "[w]hile the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls". *Id.* Thus, the basic analysis to be followed, including the use of objective evidence of secondary considerations to rebut a *prima facie* case of obviousness, remains the framework to be followed for a determination of obviousness.

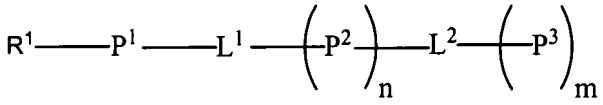
As set forth in detail below, Applicants respectfully submit that, at a minimum, the references do not teach all the limitations of the amended claims, and alternatively, there is no reasonable expectation of success.

Independent claim 118 recites a compounds having the formula:



wherein $-P^2-L^2-P^3$ is **not** a straight or branch chained saturated alkyl of from 1 to 10 carbons.

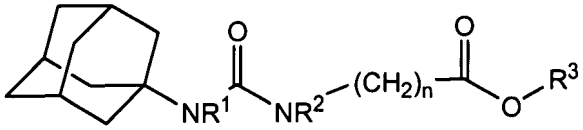
Likewise independent claim 119 recites compounds having the formula



(I)

wherein R^1 is aryl or heteroaryl and **not** adamantyl.

As stated above, Richter teaches compounds of formula:



where **Alk is a straight or branch chained saturated alkyl of from 1 to 10 carbons.**

With regard to claim 118, Richter does not teach or suggest compounds wherein $-P^2-L^2-P^3$ is anything other than a saturated alkyl of from 1 to 10 carbons, as discussed above.

Applicants assert that a skilled artisan would have no motivation to modify the teaching of Richter and substitute non-alkyl functional groups within or appended to the alkyl chain to arrive at the sEH inhibitors of the present invention. Given the disparate structures of the present compounds *vis a vis* the prior art compounds, a skilled person would have no motivation to modify their structure in the way the Examiner has contemplated.

Similarly with regard to Claim 119, Richter does not teach or suggest compounds wherein R^1 is aryl or heteroaryl.

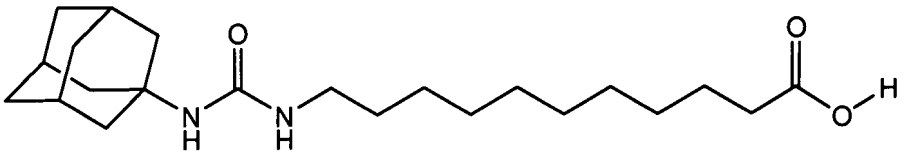
The deficiencies of Richter are not corrected by the Brocchini or Abdulla. Brocchini describes polymeric drug formulations and fails to disclose, teach or suggest compounds wherein $-P^2-L^2-P^3$ is something other than a straight or branch chained saturated alkyl of from 1 to 10 carbons, or compounds wherein R^1 is aryl or heteroaryl.

Abdulla describes the use of certain adamantyl compounds as antivirals and also fails to disclose, teach or suggest compounds wherein $-P^2-L^2-P^3$ is something other than a straight or branch chained saturated alkyl of from 1 to 10 carbons, or compounds wherein R^1 is aryl or heteroaryl. Accordingly, the Examiner is respectfully requested to withdraw this rejection with regard to these independent claims and the claims which depend thereon.

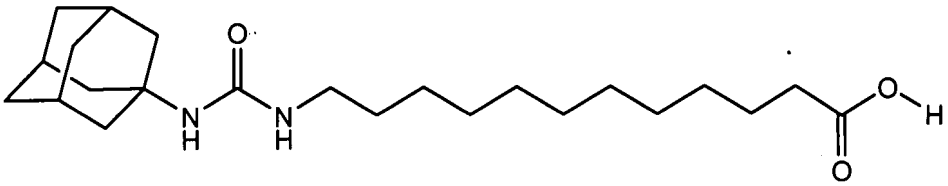
With regard to the subject matter of claims 131 and 132, the issue is whether after reading Richter, one of skill in the art would be motivated to add one or more methylene groups to the linker or would have a reasonable expectation of success with such a modification. Accordingly, Applicants respectfully traverse the rejection.

Richter reports their activity against a variety of virus cultures in the table in column 4. From that table it is evident that increasing the length of the linker between the urea and the ester decreases the viral activity (compare entries 4 and 10).

The closest compound structurally to the compounds of the present invention is:



(see Example II, col. 5). While direct comparative data between this compound and the compound of claim 132:



is not available at this time, the Applicants direct the Examiner's attention to Example 16 and the data of table 5 of the present application. As can be seen from this table, increasing the distance between the secondary ester pharmacphore and the tertiary ester pharmacaphore (compounds **549**, **635**, and **774**) maintains mouse sEH activity while increasing inhibition potency for human sEH.

As noted above, Richter does not teach or suggest adding extra methylene groups to the linker would have a reasonable expectation of success to provide compounds with

desirable activity. Rather, Richter's data teaches away from further extending the chain length to 11 or 12 carbons. At best, the Examiner's argument is that one of skill would have immediately recognized the advantages inherent in Applicants' invention. In the absence of an actual suggestion to combine the elements of the invention to achieve the results of the present invention is not sufficient to support a *prima facie* case of obviousness. The Examiner must articulate more than a hindsight recognition of the advantages of Applicants' invention to establish a motivation to combine the teachings of the cited references or a teaching of all the elements to achieve the results of the claimed invention. In view of this hindsight reconstruction of Applicants' invention, Applicants respectfully request that this rejection be withdrawn.

X. Double Patenting rejection

The Examiner provisionally rejected Claims 58, 59, 70, 105-109, and 111-114 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-11 of U.S. Patent No. 6,531,506.

The Examiner also provisionally rejected Claims 58, 59, 70, 105-109, 111-114, and 116 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-24 and 28-60 of copending Application No. 11/256,685 (the '685 application"). The Examiner further provisionally rejected Claims 58, 59, 70, 105-109, and 111-114 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over Claims 14-18, 21-23, 26-34, and 37-45 of copending Application No. 10/694,641 ("the '641 application").

In view of the amendments, the Applicants submit that the instant claims, even if embraced by the subject matter of the '506 patent are drawn to patentably distinct compounds. Accordingly, the Applicants respectfully request that the Examiner reconsider and withdraw the above rejection with respect to the '506 patent.

With respect to the '685 and '641 patent applications, the Applicants request that these rejections be held in abeyance until the claims are otherwise indicated as allowable by the Examiner.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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Attachments
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